Remarks

Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks. Claims 1 and 25 are amended. Support for the amendment of claim 1 can be found throughout the specification, such as on pages 33 and 39-40. Support for the amendment of claim 25 can be found throughout the specification, such as on page 31, lines 16-25, pages 42-45, and claims 2-5.

Following entry of this amendment, claims 1, 2, 4-6, 8-22, 25-29 and 31-34 are pending in this application.

No new matter is added. Reconsideration of the subject application is respectfully requested.

Rejection under 35 U.S.C. § 102(e)

Claims 1, 8-17 and 21 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Klinman et al. (U.S. Patent No. 6,977,245). Applicants respectfully disagree with this rejection.

The claims as amended are directed to methods of increasing an immune response to an opportunistic infection in an immunocompromised subject. The claimed methods include the steps of (a) selecting an immunocompromised subject infected with a secondary infection, (b) administering to the immunocompromised subject infected with the secondary infection a therapeutically effective amount of an immunostimulatory D oligodeoxynucleotide; and (c) assessing the immune response to the secondary infection in the subject.

Klinman et al. teaches D ODNs such as SEQ ID NO: 177. Klinman et al. also discloses administering D ODN. However, this cannot be construed to teach the specific steps in the claimed methods.

I. Klinman et al. is the work of the present inventors

The Office action only cites to the paragraph set forth in Klinman et al. that appears in column 7, lines 48-60 for any disclosure relating to steps of the presently claimed methods, such as the selection of an immunocompromised subjects. This paragraph falls under section entitled "Terms." For the Examiner's convenience, the paragraph is copied below:

> **"Immune system deficiency:** A disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response. Immune system deficiencies include those diseases or disorders in which the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response. In one specific, non-limiting example, a subject with an immune system deficiency has a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small cell), ovary, breast, prostate, colon, as well as other carcinomas and sarcomas)."

Klinman et al. lists five inventors, Dennis Klinman, Daniela Verthelyi, Ken Ishii, James J. Mond and Mayda Gursel. The present application has two inventors Dennis Klinman and Daniela Verthyli. Moreover, both the present application and Klinman et al. are assigned to the Government of the United States of America, as Represented by the Department of Health and Human Services.

A rejection under 35 U.S.C. § 102(e) can be overcome by a showing that the patent is the work of the inventors. MPEP §2136.05 states:

> ""The fact that an application has named a different inventive entity than a patent does not necessarily make that patent prior art." *Applied Materials Inc. v. Gemini Research Corp.*, 835 F.2d 279, 15 USPQ2d 1816 (Fed. Cir. 1988). The issue turns on what the evidence of record shows as to who invented the subject matter. *In re Whittle*, 454 F.2d 1193, 1195, 172 USPQ 535, 537 (CCPA 1972)."

MPEP § 715.01(a) states:

> When subject matter, disclosed but not claimed in a patent or application publication filed jointly by S and another, is claimed in a later application filed by S, the joint patent or application publication is a valid reference under 35 U.S.C. **102**(a) or (e) unless overcome by affidavit or declaration under **37 CFR 1.131** or an unequivocal declaration under **37 CFR 1.132** by S that he/she conceived or invented the subject matter disclosed in the patent or application publication and relied on in the rejection. *In re DeBaun*, 687 F.2d 459, 214 USPQ 933 (CCPA 1982).

It is further set forth in MPEP § 716.10 that:

> ...an affidavit or declaration may be submitted which attempts to attribute an activity, a reference or part of a reference to the applicant. If successful, the activity or the reference is no longer applicable.

Submitted herewith is a Declaration Under 37 C.F.R. § 1.132 signed by Dennis Klinman and Daniela Verthyli, stating that this paragraph is only a definition, and they (and not the other co-inventors of U.S. Patent No. 6,977,245) conceived of any work relating to the treatment of immunocompromised subjects that in disclosed in Klinman et al. Thus, any disclosure in Klinman et al. that is related to immune system deficiencies or immunocompromised subjects is not available as prior art in the present application. The submission of this Declaration renders the rejection moot.

II. Klinman et al. cannot anticipate the claimed methods because all of the steps in the method are not disclosed.

MPEP §2131 sets forth that "to anticipate a claim, the reference must teach every element of a claim." Klinman et al. simply does not teach every step in the claimed methods. Klinman et al. cannot be construed to disclose all of the steps in the claimed methods, as Klinman et al. does not teach either (1) the selection of subjects that are immunocompromised and have secondary infection; or (2) evaluating the response to a secondary infection.

The Office action appears to allege that since Klinman et al. can be construed to broadly teach the treatment of patients, some immunocompromised subjects (or subjects with secondary infections) would be treated. However, the populations described by Klinman et al. simply are not commensurate with the treated subjects of the presently pending claims.

The Office action acknowledges that Klinman et al. does not disclose the treatment of subjects with secondary infections. In view of this admission, it is unclear how Klinman et al. can be construed to suggest the specific selection of any subject with a secondary infection.

As discussed above, no disclosure related to the treatment of an immunocompromised subject is available from Klinman et al. Thus, Klinman et al. cannot be construed to teach or suggest the treatment of any immunocompromised subjects, let alone those subjects that also have a secondary infection.

Thus, Klinman et al. simply cannot be construed to suggest or teach the selection of a specific set of subjects that have both of these specific characteristics: (1) immunocompromised; and (2) have a distinct infection secondary to their immunodeficiency. Thus, Klinman et al. simply cannot be construed to anticipate claims 1, 8-17 and/or 21.

Claim 1 and dependent claims thereof also require that the immune response to the secondary infection be assessed. As admitted in the Office action, Klinman et al. does not describe any secondary infections. Thus, it is inconceivable how Klinman et al. can be construed to suggest the assessment of an immune response specific to the infection.

In addition, the Office action appears to allege that "evaluating" an immune response is only a mental step, such as "feeling better." The specification defines an "immune response" as "a response of a cell of the immune system, such as a B cell or a T cell to a stimulus." Thus, an evaluation is an active process, which involves assessment of the response of the cells of the immune system. Klinman et al. simply cannot be construed to teach this active step.

In view of the amendment to claim 1, and the forgoing remarks, it is clear that Klinman et al. does not anticipate claims 1, 8-17 and 21. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 1, 2, 4-6, 9-22 and 25-34 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over the combined teachings of Klinman et al and Fraternale et al.

As discussed above, any teachings in Klinman et al. related to immune system deficiencies are not available as prior art. Klinman et al. teaches D ODN, such as SEQ ID NO: 177 and their general use to induce an immune response, such as an adjuvant for a vaccine (column 18). Klinman et al. also describe K ODN.

Fraternale et al. discuss the use of combinations of protease and reverse transcriptase inhibitors in mice infected with LP-BM5, a murine model for AIDS. Fraternale et al. use mice infected with LP-BM5 to select the most effective way to administer fludarabine, a lympholytic drug, to inhibit disease progression. Fraternale et al. evaluate the efficacy and toxicity of a combination of fludarabine and AZT (an antiviral drug). Fraternale et al. conclude that sequential administration of fludarabine (a lympholytic drug) and AZT (an anti-viral agent) is most effective in reducing spleen and lymph node weights to normal values and decreasing LP-BM5 viral content. Fraternale et al. does not describe the

use of D ODN. Fraternale et al. only describe treatments effective for LP-BM5, and not for any other agents that cause an immunodeficiency. Fraternale et al. only disclose a treatment of an immunodeficiency caused by LP-PM5. No therapeutic interventions for the treatment of secondary infections are described.

As discussed below, the presently claimed methods are not obvious in view of Klinman et al. or Fraternale et al., alone or in combination.

I. There are Substantial Differences between the Cited Prior Art and the Presently Claimed Methods

Any work disclosed in Klinman et al. that relates to the treatment of an immunocompromised subject is the work of the inventors and not available as prior art.

Fraternale et al. teach drug combinations of use for treating severe immunodeficiency caused by a murine virus.

There is no motivation, absent the present disclosure, to combine Klinman et al. with Fraternale et al. Moveover, even if this impermissible combination was made, Klinman et al. and Fraternale et al. do not disclose or suggest the elements of (1) selecting a subject that is immunoconmpromised and has a secondary infection or (2) assessing an immune response to a secondary infection.

As Klinman et al. and Fraternale et al. do not teach all of the elements of the presently claimed methods, one of skill in the art could not arrive at the presently claimed methods based on the cited prior art. Thus, a *primae facie* case of obviousness simply cannot be made based on Klinman et al. and/or Fraternale et al.

II. The Cited Prior Art is from a Field that is Unpredictable

The Office action cites Fraternale et al. as providing evidence that it is obvious to combine HAART or anti-retroviral therapy with another treatment, such as a ODN, for the treatment of AIDS (see claim 4-6). A discussed in the Declaration of Daniela Verthelyi, the presently claimed methods have been tested on human PBMC in vitro and in an art-accepted macaque model of AIDS (amongst other models).

However, Fraternale et al. only disclose results obtained in a murine model system of immunodeficiency, the LP-BM5 model. Clark et al. (Viral Immunol. 14(2): 95-109, 2001, abstract submitted herewith) disclose that there are two murine models of AIDS, ts1 and LP-BM5. Clark et al.

state "LP-BM5...the murine acquired immune deficiency virus (MAIDS) model, have been studied extensively as a small animal model for HIV research, but lack many key similarities to HIV....Based on an extensive evaluation of the literature on LP-BM5 and ts1 it is concluded that the ts1 virus may serve as a better animal model to study human retrovirus infection." Similarly, Cunnigham et al. (Immunologic Research 13: 21-28, 2008, abstract attached) state "[t]he murine disease seems to display as many similarities to as it does differences from human AIDS." Thus, one of skill in the art would not believe that the results obtained by Fraternale et al. on the use of fludarabine could necessarily be combined with any other therapeutic agent.

With regard to the cited prior art, simple substitution of one element (fludarabine) for another element (D ODN) would not necessarily yield predictable results (see MPEP § 2143). In view of the unpredictable nature of the results achieved in the LP-BM5 model disclosed by Fraternale et al., a *pima facie* case of obviousness has not been made.

III. Declaration Evidence Documents One of Skill in the Art Could Not Predict the Effectiveness of the Claimed Methods Based on the Cited Prior Art

The cited prior art does not provide any suggestion that D ODNs would be effective to produce an immune response to a secondary infection. Any general disclosure of D ODNs does not provide suggestion or motivation to use them in an immunocompromised subject for the treatment of a secondary infection.

It is important to note that D ODNs are not of use in simply increasing a general immune response in immunocompromised subjects. A Declaration of Daniela Verthelyi under 37 C.F.R. § 1.132 was submitted on June 5, 2008 (hereinafter the "Declaration'). This Declaration described experiments conducted with D ODN on peripheral blood mononuclear cells (PBMC) isolated from immunocompromised subjects and healthy subjects (see page 2 of the Declaration). PBMC were exposed to D ODN using the presently claimed methods, K ODN (a different type of immunostimulatory ODN), and control ODN. The sequences of the ODNs used in the experiments are provided in the Declaration, and are also set forth in the specification on page 45.

As disclosed in the Declaration, PBMC from HIV infected and healthy subjects responded similarly to K type ODN (see Figure 1 of the Declaration), suggesting that B cells and monocytes retained their ability to respond to this form of immune stimulation. However, although D type ODN

induced a significant increase in cytokine secretion by cells from both donor populations ($p< 0.001$), the IFNγ response of healthy controls significantly exceeded that of HIV-infected subjects ($p<0.05$ and $p<0.001$, respectively, Figure 1). The reduced responsiveness to D ODN correlated directly with the number of $CD4^+$T cells among the HIV infected donors ($p<0.01$) and inversely with their viral load ($p<0.05$). On page 3 of the Declaration, data is presented documenting that D ODN were less effective at inducing the maturation of dendritic cells in PBMC from HIV infected individuals than normal donors. On page 5 of the Declaration, it is disclosed that D ODN did not produce increase in total CD4 or CD8 cells in SIV-infected macaques, such as when D35 (SEQ ID NO: 177) was administered (see page 5).

The Declaration documents that D ODNs were ineffective at inducing the production of cytokines, increasing the number of T cells, decreasing viral load, or inducing the maturation of dendritic cells in immunocompromised subjects. Thus, even if one of skill in the art, for some imperceptible reason, administered an ODN to an immunocompromised subject, they simply could not have ascertained that D ODNs would be effective to induce an immune response specific to a secondary infection in an immunocompromised subject.

Thus, it clearly is non-obvious, based on the cited prior art, to both (1) administer ODNs to immunocompromised subjects with a secondary infection or (2) assess the immune response specific to that secondary infection. The claimed methods cannot be obvious in view of Klinman et al, (or any other reference that teaches D ODN), even in view of Fraternale et al.

IV. Evidence of an Unexpectedly Superior Result

The Applicants have also provided evidence documenting the effectiveness of the claimed methods in the Declaration. The Declaration was discussed in detail in the prior response. For the Examiner's convenience, one set of results achieved using the claimed methods is described herein.

The Declaration on pages 4-5 describes the results obtained when D ODNs were evaluated in an art-accepted macaque model of HIV. Macaques that had been infected >12 months earlier with SIV Mac239 and had viral loads ranging from 0.3-28 $x10^6$ copies/ml were used. The animals were stratified based on viral load and then challenged with *L. major* metacyclic promastigotes (MHOM/IL/80/Friedlin), which is a secondary infection. Healthy macaques challenged with L. major develop cutaneous lesions characterized by erythema, induration and ulceration that peaked 25 days

after challenge and resolved within 50 days (see the Declaration, Fig. 3A). Due to their immunosuppressed state, untreated macaques developed severe progressive cutaneous lesions that did not resolve. The severity of *Leishmania* infection in SIV-infected animals treated with K ODN (another type of immunostimulatory ODN, also disclosed in Klinman et al.) was not significantly different from that of the controls.

In contrast, SIV-infected macaques treated with D ODN developed significantly smaller lesions, and their infection did not progress over time (see Figure 3A of the Declaration) as compared to controls. The animals were euthanized on day 56, and their parasite burden measured. SIV-infected monkeys treated with D ODN had a *35-fold reduction* in total parasite burden at the lesion site compared to SIV infected animals treated with control ODN or saline (see the Declaration Fig. 3B, $p<0.001$). The comparative data, both with regard to the type of ODN used (D versus K), and the type of immune response achieved (general response versus a response to a secondary infection, see III above) demonstrate the unexpectedly superior results that is achieved using the claimed methods.

The documentation of an unexpectedly superior result overcomes any *prima facie* case of obviousness based on Klinman et al. (or any other reference that describes D ODN) in view of Fraternale et al.

VI. Summary

It has been documented that the prior art does not teach or suggest all of the elements of the claimed methods to one of skill in the art. The primary reference relied upon by the Examiner has been removed as a reference to the extent that it discloses the work of the present inventors. It has also been documented that the results achieved could not have been predicted based on the cited prior art. In addition, the Applicants have provided comparative data, documenting the unexpectedly superior efficacy achieved using D ODN (as compared to K ODN, also taught in the prior art) to induce an immune response to a secondary infection in an immunocompromosed subject. Documentation has been provided that the results achieved using the presently claimed methods were both unexpected and superior.

Thus, claims 1, 2, 4-6, 9-22 and 25-34 are not obvious in view of Klinman et al and/or Fraternale et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe the present application is ready for allowance, which action is requested. If any matters remain to be discussed before a Notice of Allowance is issued, Examiner Horning is respectfully requested to contact the undersigned for a telephone interview at the telephone number listed below. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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